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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/736,188	BOWDISH ET AL.	
	Examiner	Art Unit	
	BRAD DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19,21,43-45,52-55 and 71-78* is/are pending in the application.

4a) Of the above claim(s) *44,45,54,55 and 71-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19,21,43,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/15/07,12/21/07,3/7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibits A and B*.

DETAILED ACTION

1. The amendment filed January 2, 2008, is acknowledged and has been entered. 1-5, 7-11, 13-17, 20, 22-42 and 51 have been canceled. Claims 19, 21, 43-45 and 52-55 have been amended. Claims 71-78 have been newly added.

2. Claims 19, 21, 43-45, 52-55 and 71-78 are pending in the application. Claims 44, 45, 54, 55 and 71-78 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 11, 2007.

3. Claims 19, 21, 43 and 52-53 are under examination.

Election/Restriction

4. The amendment filed January 2, 2008 presents new claims 71-78, so as to be directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

In this case, newly presented claims 71-78 are drawn to diagnostic methods to determine whether a human subject is afflicted with CLL, said methods comprising determining whether OX-2/CD200 is upregulated in said subject.

In contrast, claims in the originally elected invention are drawn to methods for treating subjects in which OX-2/CD200 is upregulated comprising determining whether OX- 2/CD200 is upregulated in a subject and administering a polypeptide that binds to OX- 2/CD200 to those subjects in which OX-2/CD200 is upregulated, wherein the polypeptide administered comprises an antibody comprising a light, chain, CDR1 region with the amino acid sequence of SEQ ID NO:12, a light chainCDR2 region with the amino acid sequence of SEQ ID NO:23, a light chain CDR3 region with the amino acid

sequence of SEQ ID NO:37, a heavy chain CDR1 region with the amino acid sequence of SEQ ID NO:55, a heavy chain CDR2 region with the amino acid sequence of SEQ ID N.O:74 and a heavy chain CDR3 region with the amino acid sequence of SEQ ID NO:93.

Notably, while the newly presented claims also comprise a method step to determine whether OX-2/CD200 is upregulated in said subject, these diagnostic methods are materially different processes comprising different method objectives, process steps, reagents used and/or endpoints from the originally prosecuted treatment methods. Notably, for example, methods to diagnose CLL by determining whether OX-2 is upregulated in a human subject would be preformed in a different patient population than the originally prosecuted invention which treats subjects in which OX-2/CD200 is upregulated. Accordingly, the methods of diagnosing require different method objectives, process steps, reagents used and the correlation of a different endpoint than the originally prosecuted methods of treating. For these reasons, where the inventions are drawn to different patient populations and measuring different correlations, each invention is expected to have different criteria for success. Accordingly, the diagnostic methods presented in new claims 71-78 are materially distinct processes comprising different method objectives, process steps, reagents used and/or endpoints that the originally prosecuted treatment methods.

Furthermore, there would be a serious burden to consider these newly added claims drawn to diagnostic methods along with the originally prosecuted treatment methods. For example, because the inventions are distinct for these reasons, each has achieved a different status in the art, as evidenced in some instances by their different classifications and/or, in other instances, by their art-recognized divergences. Accordingly, the examination of each of the inventions would require a different search. Furthermore, since these newly added claims are drawn to diagnostic methods of determining whether a human subject is afflicted with CLL while the originally prosecuted invention is drawn to treatment methods, it is submitted that such inventions raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first

paragraph. Accordingly, any need to search and consider these newly added claims, would create an undue and serious burden.

Thus, if claims drawn to methods of diagnosing CLL had been originally presented, they would have been properly restricted from the elected invention because such methods have been shown to be patentably distinct and because the examination of both inventions could not be made without serious burden. See MPEP § 803.

Since applicant has elected to prosecute methods for treating subjects in which OX-2/CD200 is upregulated in the reply filed on May 11, 2007 and the newly presented diagnostic methods are patentably distinct for the reasons set forth above, newly presented claims 71-78 have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Additionally, the Examiner notes that claims 44-45 and 54-55 have been amended so as to be only drawn to methods of treating subjects afflicted with CLL which comprise administering non-elected antibodies. Previously, these claims were drawn in the alternative to both non-elected and elected inventions and were objected to for this reason (see page 8 of the previous Office action). Accordingly, since these claims 44-45 and 54-55 are *now only drawn to non-elected* inventions, these claims have been withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b).

Information Disclosure Statement

6. The references cited in the information disclosure statements filed on October 15, 2007, December 21, 2007, and March 7, 2008, have been considered.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, Applicant's amendment and/or arguments filed January 2, 2008, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed July 30, 2007.

Grounds of Objection Maintained

Specification

8. The objection to the specification, because the use of improperly demarcated trademarks, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant has made a *bona fide* attempt to resolve this issue by appropriately amending the specification, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely HiGro®; see, e.g., page 22, last paragraph of the specification.

Again, appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. The rejection of claims 19, 21, 43 and 52-53 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 12 of the response filed October 30, 2007, Applicant has traversed this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

In the response filed January 2, 2008, Applicant appears to be arguing that amending the claims to recite "human OX-2/CD200" has obviated this rejection.

In response, Claims 19, 21, 43 and 52-53 remain indefinite because of the use of the terms "OX-2/CD200" or "human OX-2CD200" to identify the protein to which the claims are directed fails to point out with the requisite clarity and particularity the identity of the protein. Even though the protein is now designated as "human", different laboratories often use the same nomenclature to identify structurally and/or functionally distinct "human" proteins. For example, a search of "CD200" in the protein database available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=Protein, conducted on March 20, 2008, provided multiple CD200 polypeptide amino acid sequences designated from a "human" and it is unclear to which one the claim refers. Notably, one of these "CD200" polypeptides is 153 amino acids in length while another is 269 amino acids in length (see Exhibits A and B attached to this Office action) so it is apparent that these are structurally and functionally distinct proteins and it cannot be determined to which "human CD200" polypeptide the antibody must bind. Accordingly, because it is unclear and cannot be ascertained to which of the different proteins termed "OX-2/CD200" these claims are directed, it is submitted that the metes and bounds of the subject matter that is regarded as the invention is not delineated with the clarity and particularity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as permit the skilled artisan to know or determine infringing subject matter.

For these reasons and after careful and complete consideration of Applicants response, it is maintained that the claims fail to delineate the metes and bounds of the subject matter regarded as the invention with the clarity and particularity necessary to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, so as to permit the skilled artisan to know or determine infringing subject matter.

It is suggested that this issue be remedied by amending the claims to recite a limitation requiring the "human OX-2/CD200" protein to comprise a particular amino acid sequence (or other limitations that unambiguously identify the protein to which the claims are directed), which is disclosed in the specification, as filed, because such a limitation would serve to unambiguously identify the protein to which the claim is directed.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. The rejection of claims 19, 21, 43 and 52-53 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

Starting at page 12 of the amendment filed January 2, 2008, Applicant has traversed the propriety of this ground of rejection.

Applicant's arguments have been carefully considered but are not found persuasive for the following reasons:

Again, the considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

As amended, claims 19, 21 and 52 are drawn to diverse methods of treating CLL comprising determining whether a member of a structurally and functionally diverse genus of "human OX/CD200 proteins" is upregulated in a human subject afflicted with CLL and then administering to subjects in which "OX/CD200" is upregulated a member of a structurally and functionally diverse genus of "antibodies" that bind a structurally and functionally diverse genus of "human OX/CD200 proteins", wherein the antibody is administered in an amount effective to "inhibit an immune-suppressing effect of OX-2/CD200". Claims 43 and 53 are drawn to the methods of claim 19, wherein the antibody administered comprises a light chain CDR1 region comprising SEQ ID NO: 12; a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 23; a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 37; a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 55; a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 74; and a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 93, said antibody administered in an amount effective to "inhibit an immune-suppressing effect of OX-2/CD200".

In the response filed January 2, 2008 Applicant appears to be arguing that the amended claims comply with the written description requirement because the designation "human OX-2/CD200" coupled with the claim language "***an*** immune suppressing effect of OX-2/CD200" is sufficient to define a fully characterized antigen that one of skill in the art would immediately envision or recognize. Furthermore, Applicant argues that they are not claiming the full genus of CD200 antibodies, but a subgenus that "inhibits an immune-suppressing effect of OX-2/CD200". Based on this, Applicant appears to be arguing that the claimed methods comply with the written description requirement.

As a first point and as explained in the previous Office action, since the art teaches a polypeptide designated "OX-2/CD200" protein, which has multiple immune

suppressing effects while the specification only teaches one antibody which comprises a light chain CDR1 region having a comprising SEQ ID NO: 12; a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 23; a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 37; a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 55; a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 74; and a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 93 that results in inhibition of a downregulation of IL-2 and IFN-γ caused by expression of OX-2/CD200 in transfected cells (see Figures 14-16 and page 29), it is submitted that the specification does not adequately describe which particular "immune suppressing effects of OX-2/CD200" that the "antibody" administered to the subject necessarily has.

In further response, as set forth in the above rejection of the claims under 35 U.S.C. 112, second paragraph, the structural characteristics of the protein designated "human OX-2/CD200" in the claims cannot be determined and therefore there can be no correlation of any particular identifying structural feature of these mutant forms of factor VII, which is shared by members of the genus, and any particular identifying function that is also shared by at least a substantial number of these mutant forms of factor VII. Notably, as explained in the above rejection of the claims under 35 U.S.C. 112, second paragraph, the term "human OX-2/CD200" identifies multiple structurally distinct polypeptides that are not disclosed as sharing any particular structural feature in the specification as filed. For example, as evidenced by the attached Exhibit A and Exhibit B, one of these "human" CD200 polypeptides comprises 153 amino acids, while another comprises 269 amino acids. Furthermore, as explained in more detail in the below rejection of the claims under 35 U.S.C. 112, first paragraph amending the claims to recite "***an*** immune-suppressing effect of OX-2/CD200" appears to introduce matter not supported in the specification as originally filed, so it is submitted that such a limitation cannot be a particularly identifying functional feature of a "human CD200" antigen. Accordingly, how would one of skill in the art immediately envision or recognize that the term "human OX-2/CD200" defines a "fully-characterized antigen"? For example, if one of skill in the art were given two OX-2/CD200 polypeptides one of skill in the art could

not immediately determine whether the polypeptide was the "human OX-2/Cd200" polypeptide referred to in the claimed methods or if an antibody that binds to either of the polypeptides could be used in methods of treating CLL in a human subject.

Notably, contrary to Applicant's assertions otherwise, the Examiner is not submitting that only a single antibody having six specifically defined CDR sequences may be claimed. First, these claims are directed to methods of treating CLL and not a product *per se*, i.e., an antibody. Therefore, the specification must adequately describe the claimed methods. As set forth in the previous Office action, the specification only adequately describes the scFv-9 antibody clone as being able to inhibit the downregulation of IL-2 and IFN-γ caused by upregulated expression of OX-2/CD200 caused by transfection of an OX-2/CD200 cDNA into an *in vitro* mixed lymphocyte reaction (see e.g., Example 3). Accordingly, as explained in the previous Office action, while one of skill in the art would recognize that antibodies comprising the 6 CDRs of the scFv-9 antibody, such as the antibodies recited in instant claim 43, would inhibit the downregulation of IL-2 and IFN-γ caused the expression of human OX-2/CD200 encoded by that cDNA in a mixed lymphocyte reaction (See page 28 of the specification), they would not immediately envision which other immune suppressing effects such antibodies might have. Thus, since, as amended, the claims are drawn to inhibiting "***an*** immune-suppressing effect of OX-2/CD200" it is maintained that the specification does not adequately describe the claimed methods.

As explained in the previous office action, one of skill in the art would not conclude that the scFv-9 antibody is representative of all antibodies that bind any human OX-2/CD200 protein which are encompassed by the claimed methods. For example, Gorczynski et al (of record) teach that OX-2/CD200 proteins cause multiple effects that suppress the immune system, including down-regulating IL-2 and IFN-γ as well as up-regulating the anti-inflammatory cytokine IL-10.

Given the lack of particularity with which the genera of "human OX-2/CD200 proteins", antibodies that bind "human OX-2/CD200" and "immune suppressing effects" of human OX-2/CD200 proteins, to which the claims are directed, are described in the

specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the genus of "antibodies that bind human OX-2/CD200" that have the ability to "inhibit an immune suppressing effect of OX-2/CD200" or which immune suppressing effects that an antibody which comprises a light chain CDR1 region having a comprising SEQ ID NO: 12; a light chain CDR2 comprising the sequence set forth in SEQ ID NO: 23; a light chain CDR3 comprising the sequence set forth in SEQ ID NO: 37; a heavy chain CDR1 comprising the sequence set forth in SEQ ID NO: 55; a heavy chain CDR2 comprising the sequence set forth in SEQ ID NO: 74; and a heavy chain CDR3 comprising the sequence set forth in SEQ ID NO: 93 would inhibit besides inhibiting the down-regulation of IL-2 and IFN-γ in a mixed lymphocyte reaction resulted. (Figure 15 and page 28 of the specification); and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Accordingly, after careful and complete consideration, contrary to Applicant's arguments, for these reasons and as explained more fully in the Office action mailed July 30, 2007, the specification as filed would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed and this rejection is maintained.

13. The rejection of claims 19, 21, 43 and 52-53 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

At page 15 of the amendment filed January, Applicant has traversed this ground of rejection and appears to be arguing that the claimed methods are enabled by specific guidance in the specification that "clearly demonstrates that anti-OX-2/CD200 antibodies are useful therapeutic agents for treating CLL in which OX-2/CD200 is upregulated". In particular, Applicant points to Example 3, starting on page 26 of the

specification which discloses that cells transfected with a CDNA that encodes an OX-2/CD200 polypeptide results in down-regulation of IL-2 and IFN-γ in an *in vitro* mixed lymphocyte reaction assay and that an scFv-9 antibody converted to full IgG can inhibit the down-regulation of IL-2 and IFN-γ caused in this *in vitro* mixed lymphocyte reaction assay. Therefore, at page 17 of the response filed January 2, 2008 ,Applicant submits that while this is an *in vitro* assay, the assay replicates what occurs *in vivo* and that anti-OX-2/CD200 would be expected to similarly affect the *in vivo* immune response. Thus, Applicant appears to be arguing that this *in vitro* assay which monitors IL-2 and IFN-γ levels is reasonably "predictive of the *in vivo* anti-tumor effects of the anit-OX-2/CD200 antibodies".

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Contrary to Applicant's arguments, the specification, as filed, would not reasonably enable the skilled artisan to use the claimed method for treating CLL in a human subject without undue and/or unreasonable experimentation.

As amended, the claims are herein drawn to methods of treating CLL in human subjects afflicted with CLL that have upregulated OX-2/CD200 by administering to said subjects an antibody or antigen-binding fragment thereof that binds to human OX-2/CD200 or an antibody comprising the 6 CDRs of the scFv-9 antibody, i.e., a light chain CDR1 region consisting of SEQ ID NO:12, a light chain CDR2 region consisting of SEQ ID NO:23, a light chain CDR3 region consisting of SEQ ID NO:37, a heavy chain CDR1 region consisting of SEQ ID NO:55, a heavy chain CDR2 region consisting of SEQ ID NO:74 and a heavy chain CDR3 region consisting of SEQ ID NO:93 in an amount effective to inhibit an immune-suppressing effect of OX-2/CD200.

Therefore, in response to Applicant's argument's, while Applicant asserts that the *in vitro* assay presented as Example 3 is reasonably predictive of anti-OX-2/CD200 antibodies having an *in vivo anti-tumor* effect in human CLL patients, the Examiner disagrees because the specification has not established any nexus between the scFv-9 antibody converted to full IgG which is shown on Example 3 as being able of inhibiting

the down-regulation of IL-2 and IFN-γ production in an *in vitro* mixed lymphocyte reaction assay specification and *in vivo* methods of treating CLL in human patients with any anti-OX-2/CD200 antibody, or more particularly an antibody comprising the 6 CDRs of the scFv-9 antibody, i.e., a light chain CDR1 region consisting of SEQ ID NO:12, a light chain CDR2 region consisting of SEQ ID NO:23, a light chain CDR3 region consisting of SEQ ID NO:37, a heavy chain CDR1 region consisting of SEQ ID NO:55, a heavy chain CDR2 region consisting of SEQ ID NO:74 and a heavy chain CDR3 region consisting of SEQ ID NO:93. Notably, as set forth in the previous Office action the specification provides no evidence or scientific reasoning that would suggest that antibodies comprising the 6 CDRs of the scFv-9 antibody inhibit tumor growth *in vitro* or *in vivo*. Accordingly, why would one of skill in the art conclude that the results that an scFv-9 antibody converted to full IgG could inhibit the down-regulation of IL-2 and IFN-γ production in an *in vitro* mixed lymphocyte reaction assay is reasonably predictive of the genus of anti-OX-2/CD200 antibodies having an *in vivo* anti-tumor effect in human subjects afflicted with CLL? One of skill in the art would not make the leap to treating human CLL patients by administering any anti-OX-2/CD200 antibody or even by administering the scFv-9 antibody converted to full IgG to human subjects based on this *in vitro* data because further undue and/or unreasonable experimentation would be required before one of skill in the art could reasonably predict whether such antibodies would be effective to treat human CLL patients with upregulated OX-2/CD200. In further response, as evidenced by Chen et al (of record) in the previous Office action, only antibodies that specifically bind to human OX-2/CD200 in its N-terminal region have the ability to inhibit the down-regulation of IL-2 by human OX-2/CD200 (see entire document, e.g., page 286, Figure 5B), while antibodies that specifically bind in the C-terminal region do not have this ability. Therefore, because the specification had not established a nexus between anti-OX-2/CD200 antibodies or the particularly described scFv-9 antibody and tumor growth inhibition, one of skill in the art could not reasonably extrapolate the teachings of the specification to methods of treating CLL in human subjects without undue and/or unreasonable experimentation.

Secondly, Applicant appears to be arguing that the specification was enabling of the claimed methods of treating human CLL patients with upregulated OX-2/CD200 as of their filing date because later *in vivo* experiments presented in US Patent Applications 10/894,672 and 11/171,567, published as US 2005/0074452 and US 2006/0057651, respectively, demonstrate that an anti-CD200 can inhibit tumor growth in an animal model.

In response, Applicant is reminded that supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See M.P.E.P. § 2164.05(a). Notably, the claimed methods of treating human CLL patients need to be enabled as of their filing date and Applicant does not explain how the data presented in the later filed applications demonstrates that the claimed methods were enabled as of their filing date.

Finally, Applicant appears to be arguing that the references cited by the Examiner would not cause one of skill in the art to doubt the predictive value of the *in vitro* experimental results provided in the instant application to the claimed methods of treating CLL in human subjects (see page 17 of the response filed January 2, 2008).

In response, the Examiner disagrees because the references cited speak to the unpredictability in the field of cancer drug discovery which is applicable in the current case because the specification, as filed, only establishes that an scFv-9 antibody converted to full IgG can inhibit the down-regulation of IL-2 and IFN-γ in an *in vitro* mixed lymphocyte reaction assay and for the reasons outlined above and in the previous office action does not provide any specific, non-general guidance that would allow one of skill in the art to treat CLL patients with upregulated OX-2/CD200 with an anti-OX-2/CD200 antibody or an antibody comprising the 6 CDRs of the scFv-9 antibody. Therefore, as evidenced by the references in the previous Office action, one of skill in the art would be subject to undue experimentation to practice such methods because one of skill in the art could not reasonably extrapolate the *in vitro* data presented to the claimed methods of treating patients afflicted with CLL.

For example, while the Applicant asserts that Zips et al is not pertinent to the instant application because the instant application is directed to leukemia, a blood borne cancer, while Zips et al is only speaking to the unpredictability of extrapolating *in vitro* methods to treating solid tumors, the Examiner disagrees. Notably, Zips et al teach that a tumor consists "of interacting malignant and non-malignant cells and therefore "prediction of drug effects in cancer patients based solely on in vitro data is not reliable and further evaluation in animal tumor systems is essential" (see page 3, right column). Therefore, why doesn't Zips speak to the unpredictability of extrapolating *in vitro* methods to the claimed methods of treating CLL in human subjects? Notably, blood borne cancers such as CLL also consist of malignant cells that interact with non-malignant cells, so *in vitro* data generated with blood borne cancer cell lines suffer from the reliability problems outlined by Zips et al, as well.

Notably, in the instant case, the extrapolation required for one of ordinary skill in the art is from an *in vitro* assay that only establishes that a scFv-9 antibody converted to full IgG can inhibit the down-regulation of IL-2 and IFN-γ to in vivo methods of treating a human subject afflicted with CLL. One of skill in the art would not consider the *in vitro* data presented in the instant specification to be a credible model to enable the claimed methods of treating CLL in patients afflicted with CLL because as evidenced by Gura and Zips et al (of record) in the previous Office action, the state of the art was such that those of skill in the art readily recognized the unpredictability of extrapolating *in vitro* cell line data to human treatments. In this case, the instant specification does not present evidence that the scFv-9 antibody converted to full IgG inhibits CLL tumor growth *in vitro* so one of skill in the art would be subject to undue and/or unreasonable experimentation to practice the claimed methods of treating CLL in human subjects afflicted with CLL by administering an anti-OX-2/CD200 antibody or an antibody comprising the 6 CDRs of the scFv-9 antibody to patients with upregulated OX-2/CD200.

Therefore, for these reasons and as explained more fully in the previous Office action, upon careful and complete consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit

decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) and after careful and complete consideration of Applicant's response and arguments, the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. The submission of a statement under 37 CFR § 1.78(c) by Assignee indicating that U.S. Patent Application Nos. 10/736,188 and 10/379,151 were commonly owned or subject to an obligation of assignment to Alexion Pharmaceuticals, Inc. at the time the later inventions were made, is acknowledged.

16. The provisional rejection of Claims 19, 21, 43 and 52-53 on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 50-54 and 70 of copending Application No. 10/379,151, is maintained for the reasons of record, as explained in the previous Office action.

At page 17 of the amendment filed January 2, 2008, Applicant has noted that both Applications are currently pending and requested that this issue be held in abeyance.

This rejection will be maintained until it is appropriately resolved.

New Ground of Rejection

Claim Rejections - 35 USC § 112

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 19, 21, 43 and 52-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a NEW MATTER rejection.

As amended claim 19 now recites the phrase "an immune–suppressing effect of OX-2/CD200" which differs from the previously recited phase, "the immune-suppressing effect of OX-2/CD200".

Applicant has indicated that support for the amendment to claim 19 can be found throughout the specification, but in particular at page 8, lines 3-9 and in Figure 13 (see, e.g., page 10 of the amendment filed January 10, 2008).

Contrary to Applicant's assertion, however, it does not appear that the specification, including the claims, as originally filed, provides written support for the language of the claims.

The specific disclosures at paragraphs page 8, lines 3-9 is merely a description of Figure 13 and presents the following disclosure:

> Fig 13. shows that three scFv antibodies bind specifically to 293-EBNA cells transiently transfected with a human OX-2/CD200 cDNA clone. A OX-2/CD200 cDNA was cloned from CLL cells by RT-PCR and inserted into the mammalian expression vector pCEP4 (Invitrogen). PCEP4-CD200 plasmid or the corresponding empty vector pCEP4 was transfected into 293-EBNA cells using Polyfect reagent (QIAGEN). Two days after transfection, the cells were analyzed for binding to scFv antibodies by flow cytometry.

Notably, this disclosure does not appear to support the broader phrase "an immune-suppressing effect of OX-2/CD200" as instantly recited. Furthermore, support for the broader genus encompassed by the phrase "an immune-suppressing effect of OX-2/CD200" as compared to "the immune-suppressing effect of OX-2/CD200" could not be found in the specification as filed. Therefore, it is primarily because of any such difference in scope that might be read into the claims, as amended, relative to the disclosure, as filed, that it is submitted that Applicant's amendment has introduced new concepts, thereby violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Given the apparent difference in the breadth of the claims and that of the pertinent disclosures, it is submitted that the amendment has introduced new concepts, violating the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Otherwise this issue might be resolved if Applicant were to point to other disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the instant claims.

Conclusion

19. No claim is allowed.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
March 27, 2008